Global Regulatory Policy

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Food and Drug Administration
5630 Fishers Lane, Rm. 1061
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RE: [Docket No. 2004N-0018] – Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application

Merck & Co., Inc. is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's research and development pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck supports regulatory oversight of pharmaceutical product development and welcomes rules for the acceptance of clinical trial data, resulting from trials conducted outside of the United States, that are based on sound clinical and scientific principles and good judgment. As a leading pharmaceutical company, Merck has extensive experience in thoroughly evaluating our products throughout discovery, clinical performance, approval and marketed life to assure that they continue to provide health benefits with minimum risk. Therefore, we are well qualified to comment on the proposed rule issued on June 10, 2004[1]. Herein, we are providing comment on the proposed rule entitled: *Human Subjects Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application.*

General Comments

We commend the FDA for its efforts in the development and proposed revision of the rule for industry on acceptance of foreign clinical study data as support for an investigational new drug application (IND) or marketing application for a drug or biologic. The acceptance of these data based on the conduct of well-designed and adequately controlled studies in accordance with Good Clinical Practice (GCP) is fully supported by Merck. Conducting studies in countries outside of the US is often the only alternative when investigating treatments or preventative therapies for diseases that are uncommon in the United States. Additionally, business reasons such as determining

[1] 69 FR 32467, Docket No 2004N-0018

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product launch strategies may drive the timing and geographical locations specified in the overall clinical development plan. We believe that if these studies are conducted in accordance with GCP, they are suitable for submission to the FDA in support of an IND and marketing approval. Acceptance of clinical trial data resulting from studies conducted outside of the US IND is a step forward toward fostering product development using innovative approaches, as promoted in the FDA's critical path document. The reason why clinical studies are not accepted by the Agency should not be due to the geographical location often driven by a misalignment of the timing of the foreign clinical study with the timing for filing the IND.

The proposed rule would benefit from a slight clarification to reduce potential regulatory burden. We propose the following wording be added to the proposed rule:
The information to be provided in support of the IND does not need to be submitted to FDA throughout the study. The supporting information may be provided at the time the clinical study report is filed to the FDA in support of an NDA and/or made available upon request.

A major revision to the proposed rule is an important step toward international harmonization. Changing the reference from the Declaration of Helsinki to good clinical practice (GCP) reflects the adoption of the International Council on Harmonization (ICH) E6: Consolidated Guideline on Good Clinical Practice, as a global standard for the conduct of sponsored clinical research. If clinical studies are conducted in regions that have adopted the ICH guideline, it should be sufficient to provide reference to ICH as governing the study conduct. If ICH E6 is adopted in the region where the trial is conducted, gaining consent and clinical monitoring are as specified by the requirements in E6.

Specific Comments

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(b) *Supporting information.*

(1) The investigators qualifications, (2) A description of the research facility. Information that must be provided to verify the investigator's qualifications or the description of the research facility should be similar to that currently provided to the FDA by pharmaceutical sponsors for studies conducted under an IND. We do not support additional regulatory burden being applied to these items.

(6) The names and qualifications for the members of the IEC that reviewed the study. Additional supporting information proposed in the draft rule concerns the names and qualifications for the members of the IEC that reviewed the study protocol. We anticipate difficulty in obtaining this information as, in many cases; the members of international review boards are not publicly identified due to local

privacy regulations. Further, providing the names of the members does not, theoretically, disclose which members actually participated in the review of the research. Hence, the value of proving names without designation of whether a quorum participated in the vote, whether members were appropriate would not, in our opinion, further the reliability of the data. This detail would only be available in the meeting minutes generated by the IRB (which are not routinely available to sponsors for confidentiality reasons). For these reasons, we propose that providing a statement from the IEC that it is organized and operates according to GCP and the applicable laws and regulations should be acceptable.
(7) A summary of the IEC's decision to approve or modify and approve the study, or to provide a favorable opinion. We propose that the currently available IEC review and approval should continue to be documented by receipt of the approval letter from the committee. This provides an adequate summary of their opinion and, as such, should be acceptable to the FDA. Currently, these letters are usually issued in the local language of the country in which the study is conducted and official translations will be provided. Clarity is sought, however, whether approvals would be expected for only the original protocol, or for all protocol amendments as well.

Sections (3) A detailed summary of the protocol and results of the study... (8) A description of how informed consent was obtained... (10) A description of how the sponsors monitored the study... (11) A description of how investigators were trained... We have similar comments on these sections; all related to adoption of ICH standards. Along with other global pharmaceutical companies, Merck has adopted ICH standards for conducting clinical research globally. Included in these standards is the adoption of ICH E3: The Structure and Content of Clinical Study Reports. It is requested that FDA modify the requirements in the proposed rule to clearly indicate that it is acceptable to follow the requirements of ICH E3, as noted in the following examples:

ICH E3 Annex I "Synopsis" provides a template for the synopsis or summary of a clinical study. The detailed summary requested in Section b(3) of the proposed rule should reference this Annex.

ICH E3 contains detailed sections describing Patient Information and Consent including a description of any incentives that may have been provided, which would apply to Section b(8) of the proposed rule. Sections b (10) and (11) pertain to monitoring of the study and investigator training and are also reflected in ICH E3. A sponsor should be able to provide a statement in the clinical study report which indicates that the sponsor provided training to the principal investigators on GCP compliance.

ICH E3 describes data quality assurance, specifically; the use of standard terminology and the collection of sound data. Therefore, the intent of sections b(10) and (11) should be covered by reference to ICH E3 Section 9.6 "Data Quality Assurance".

Finally, ICH E3 clearly describes the format and content of the protocol and protocol amendments in an appendix (16.1.1) and should be referenced in section b (11) of the proposed rule. The written investigator commitments are usually included in the investigator signature page of the protocol; which is described in ICH E3 Appendix 16.1.1. ICH E6 Good Clinical Practice Section 8.2.2 requires archival of the individual investigators' signature pages in the sponsor's trial master file. It should suffice to only require a description of how the investigator commitment was obtained to comply with GCP and the protocol and eliminate the proposed requirement to submit an individual form for each participating investigator.

Conclusion

We commend the Food and Drug Administration for issuance of revisions to the rule concerning foreign clinical studies not conducted under an IND. The revisions to the rule promote harmonization and an understanding of the requirements for the conduct of the foreign clinical study to allow its acceptance by the FDA. We appreciate the opportunity to share our comments with respect to FDA's Proposed Rule: *Human Subjects Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application.* Please do not hesitate to contact me, should you have any questions.

Sincerely,

Donald M. Black, MD, MBA
Vice President
Global Regulatory Policy